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Use of comedication in patients with hepatitis C and addiction or drug abuse treated with direct-acting antivirals: implication in drug-drug interactions

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INTRODUCTION

- Direct-acting antivirals (DAA) may interact with the usual treatment of patients with chronic hepatitis C infection.[1–3]
- An exhaustive assessment regarding the risk of drug-drug interactions (DDIs) is recommended in patients starting the DAA therapy and the administration of other comedications.[4–6]
- In previous studies, we analyzed DDIs in the general population, but this sub-analysis focuses on patients infected with hepatitis C virus (HCV) with addiction to substances or drug abuse.

AIM

- The objective is to describe drug abuse, frequent comorbidities, comedication and the associated risk of DDIs in patients with addiction to substances or drug abuse and hepatitis C, treated with direct-acting antivirals.

METHODS

- This is a retrospective and observational study based on the electronic medical reports from the BIG-PAC® database.
- The study population was ≥18 years old HCV patients treated with sofosbuvir/velpatasvir [SOF/VEL] or glecaprevir/pibrentasvir [GLE/PIB] between 2017 and 2020.
- Demographic variables were collected: age, sex; clinical: degree of fibrosis, presence of addictions or substance abuse; pharmacotherapeutic; and adverse events; type of direct antiviral prescribed, and comedication used.
- Confidence intervals (CI) of 95% were used to estimate the population parameters. For the analyses, the statistical software IBM/SPSS was used. Values of $p<0.05$ were considered statistically significant.
- Possible DDIs with DAAs were evaluated using the HEP interaction database (University of Liverpool).[12]
- Comedications recorded by the anatomical therapeutic classification (ATC). DDIs were classified according to the strength of interaction and the predicted clinical outcome.

Predicted clinical outcome	
↑comedication ↑DAA (↑↑)	Possible impact on safety
↑comedication (↑)	
↓DAA (↓)	Possible impact on efficacy

- Adverse events (AEs) potentially connected to DDIs were identified by the ICD-9-CM, codes 990–995 and E930–E949 during DAA treatment period. The comedications associated to the AEs and their classification were recorded.

STRENGTH OF INTERACTION CONTRAINDICATED | SIGNIFICANT INTERACTION | WEAK INTERACTION | NO INTERACTION

RESULTS

Patients' characteristics

- The study included 985 patients with HCV infection and addiction to substances or drug abuse. 450 patients were treated with SOF/VEL (mean age: 53 years; men: 65%) and 535 with GLE/PIB (mean age: 50 years; men: 65%). SOF/VEL patients had higher fibrosis status than GLE/PIB ones (F3/4: 41.8% vs. 29.7%, respectively; $p<0.001$).
- The percentage of patients with addiction or substances abuse are described in Table 1. SOF/VEL patients consumed more opioids than GLE/PIB patients (13% vs 9%, $p<0.05$, respectively).
- The mean number of comedications prescribed was 3.9 for SOF/VEL and 2.1 for GLE/PIB ($p<0.001$).

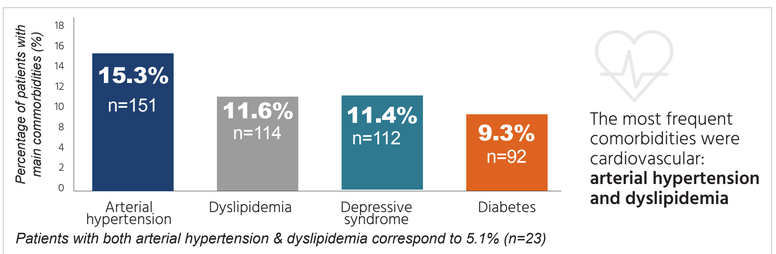
Table 1. Prevalence of additions in the study population

Study groups	GLE / PIB	SOF / VEL	Total	P value
Number of patients, %	535 (54.3%)	450 (45.7%)	985 (100%)	
Chronic alcoholism	105 (**20%**)	110 (**24%**)	215 (**22%**)	0.068
Opioids	47 (**9%**)	60 (**13%**)	107 (**11%**)	0.022
Sedatives-anxiolytics	136 (**25%**)	140 (**31%**)	276 (**28%**)	0.048
Cannabis	235 (**44%**)	198 (**44%**)	433 (**44%**)	0.981
Cocaine	142 (**26%**)	116 (**26%**)	258 (**26%**)	0.786
Heroin	77 (**14%**)	80 (**18%**)	157 (**16%**)	0.148

The most prescribed cardiovascular comedications

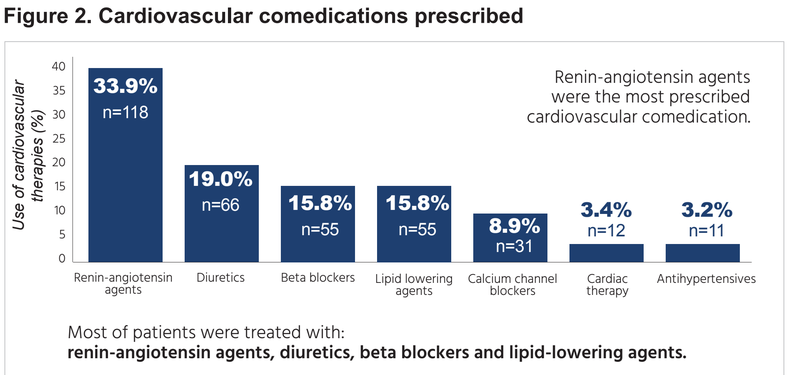
- The most frequent comorbidity was the cardiovascular (arterial hypertension, 15.3% & dyslipidemia, 11.6% respectively); followed by depressive syndrome (11.4%) and diabetes (9.3%) (Figure 1).

FIgure 1. Prevalence of comorbidities in the study population.



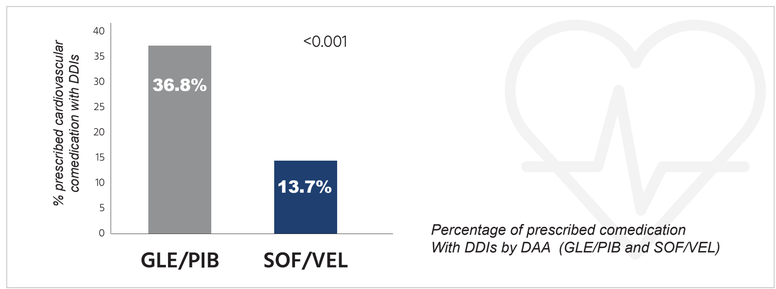
- The more prescribed cardiovascular comedications were renin-angiotensin agents (33.9%), diuretics (19%), beta blockers (15.8%) and lipid-lowering agents (15.8%) (Figure 2).

Figure 2. Cardiovascular comedications prescribed



- Regarding DDIs, GLE/PIB patients had more potential DDIs with cardiovascular comedication than SOF/VEL patients (36.8% vs 13.7% respectively, $p<0.001$) (Figure 3); being enalapril (4.4%) the most prescribed cardiovascular drug.

Figure 3. % prescribed Cardiovascular comedications with DDIs with DAA



- As renin-angiotensin agents were the most prescribed cardiovascular comedication, this subanalisis will focus on this therapeutic group.
- Regarding DDIs, about forty percent (42.6%) of patients treated with renin-angiotensin agents patients and GLE/PIB were at risk of potential DDIs, whereas none of them were at risk with SOF/VEL (0.0%) (table 2 and Figure 4).

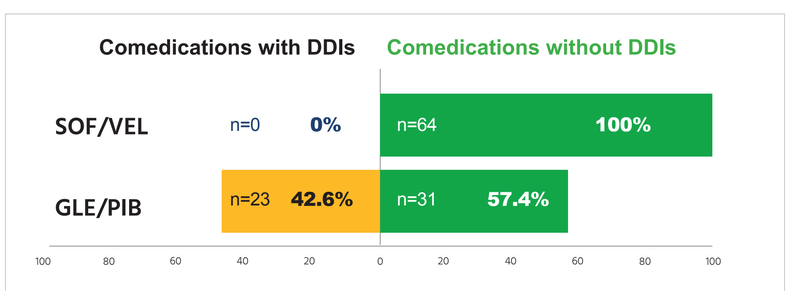
Table 2. Strength of potential percentage of patients at risk of DDIs and predicted clinical outcomes in cardiovascular drugs (CV).

Therapeutic CV group/ DAA	GLE / PIB N*=54	SOF / VEL N*=64
Renin-angiotensin agents (n**/N [%])	↑ Enalapril (17/54 [31.5%])	Enalapril (26/64 [40.6%])
	↑ Irbesartan (2/54 [3.7%])	Irbesartan (0/64 [0.0%])
	↑ Olmesartan (3/54 [5.6%])	Olmesartan (2/64 [3.1%])
	↑ Telmisartan (1/54 [1.9%])	Telmisartan (2/64 [3.1%])
TOTAL patients at risk DDIs increasing comedication concentration (n**/N [%])	**↑ (23/54 [42.6%])**	**(0/64 [0.0%])**

Only renin-angiotensin comedication showing DDIs with any of the DAA were included in this table.

*↑:Increase comedication. **n****: number of patients on treatment with the corresponding drug. **N***: number of patients who had prescriptions renin-angiotensin comedications. **Percentages (%)** were estimated as the number of patients prescribed each active ingredient (n**) with DDIs with any pDAA, over the total population receiving renin-angiotensin drugs (N*) .*

FIgure 4. Percentage of potential DDIs of DAAS with Renin-angiotensin agents

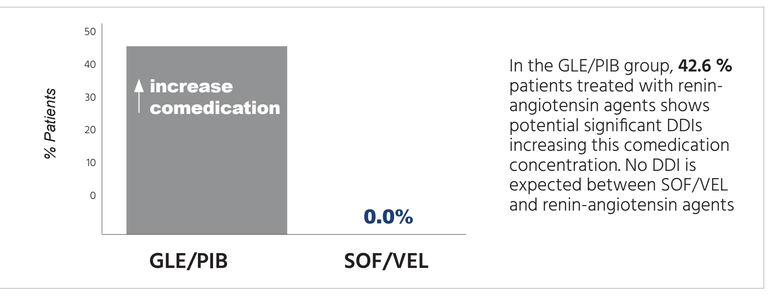


Potential DDIs: drug-drug interactions; n: number of patients prescribed renin-angiotensin agents. Percentages (%) of prescribed rennin-angiotensin comedication with or without potential DDIs with DAAs, calculated over the total renin-angiotensin agents' prescription.

Outcomes of potential DDIs and Adverse events (AE) associated to renin-angiotensin agents

- Potential DDIs with renin-angiotensin agents and GLE/PIB lead to potential increase in comedication exposure in 42.6% of cases, with a possible impact on safety (Table 2 and Figure 5).

Figure 5. Outcome of potential DDIs with renin-angiotensin



Percentage of patients treated with renin-angiotensin at risk DDIs increase comedication. Orange colour means potential significant interaction.

- 1 AE for the renin-angiotensin agents group was reported by a Family doctor:
  - This AE was associated to enalapril within the GLE/PIB treated patients (1AE/17 patients, 5.9%) (Table 3).
  - While no AE was reported for the SOF/VEL treated group (0 AE/26 patients; 0%) (Table 3).

Table 3. Summary of reported adverse events (AE) by DAA.

Associated comedication to AE		GLE / PIB	SOF / VEL
Renin-angiotensin agents	Enalapril (%AE; n/N), [AE]	5.9%; 1/17 [respiratory] / Dose reduction	0%; 0/26 [No AE] No Action

AE: adverse events reported; n: number of patients with reported AE; N: number of patients with the corresponding prescription comedication.

CONCLUSIONS

- Cardiovascular diseases (arterial hypertension and dyslipidemia) were the most frequent comorbidities in patients with HCV infection and addiction to substances or drug abuse.
- Renin-angiotensin comedication was the most prescribed cardiovascular comedication. SOF/VEL doesn't interact with renin-angiotensin agents.
- Potential DDIs between renin-angiotensin agents and GLE/PIB, led to an increase in the comedication exposure, with a possible impact on safety.

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DISCLOSURES

Speaking/consulting/research: JT (AbbVie, Gilead Sciences, MSD), AGH (AbbVie, Gilead Sciences), RM (AbbVie, Gilead Sciences, Janssen, MSD, ViiV Healthcare), ASM (Atrys Health employee). Gilead employees: MM, CA and CH.

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